Peer Review
Experimental Toxicology Division
N H E E R L

MODELING

Application of Physiologically based Pharmacokinetic Modeling (PBPK) to the Risk Assessment of Malathion Used as Treatment for Head Lice in Children

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11 NHEERL, US EPA, ORD, ETD, RTP, NC; 2 NERL, US EPA, ORD, EDRB, LV, NV

ENVIRONMENTAL ISSUE

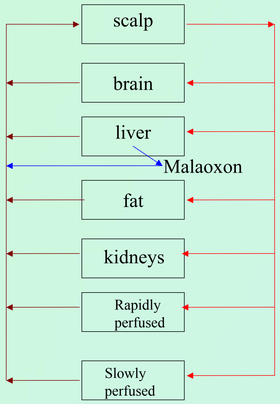
•The US EPA needs to address potential health risks which affect children as a susceptible population.
•A tool is needed that will predict internal target dose and at the same time consider differences between children and adults.
•This same tool can also be extended to address extrapolation across different routes of exposure.
•Ovide™ is a shampoo preparation containing the pesticide ingredient, malathion.
•Within EPA, the Office of Pollution Prevention and Toxics (OPPT) requested ORD scientists for assistance in developing a predictive pharmacokinetics model for this particular application.

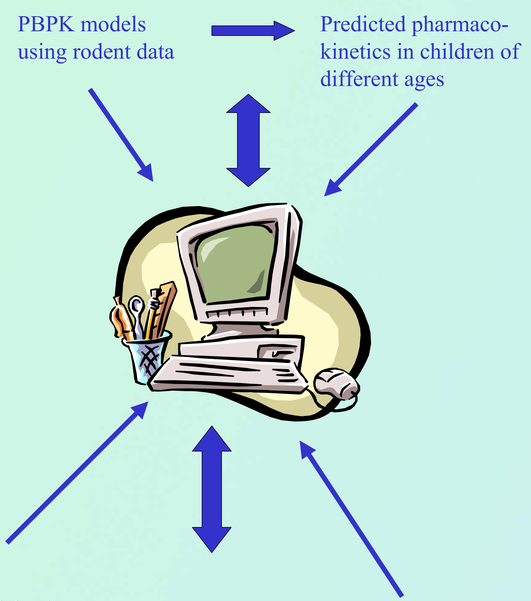
OBJECT/STUDY GOAL

•The prescribed use specifies 12 hours of treatment on the scalp.
•Basically, children of different ages will be the population of concern.
•These researchers chose to develop a PBPK model to be used as the predictive tool.
•The computer simulation studies included children 3, 9, and 18 years of age, both genders included.

METHODS

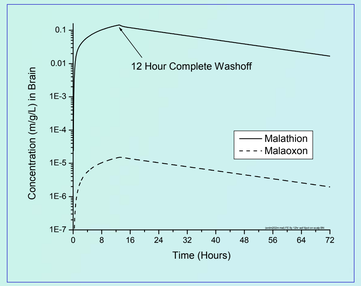
• A PBPK model includes all organs playing a role in malathion's distribution and disappearance.
•The target organ for toxicity is also included.
•Physiological changes across life stages are included in the model.
•Malathion-specific partitioning into organs was calculated with tissue-composition equations.
•Metabolic conversion to the toxic species was included.
•Application of rodent data and extrapolation to humans is possible.



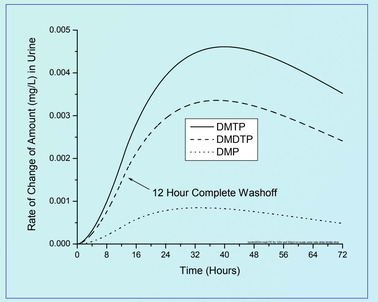


SAMPLE SIMULATIONS FOR A 9 YEAR OLD GIRL

Target Concentration of malathion and the toxic species, malaoxon



Urinary rates for selected metabolites for same 9 year old girl



Summary

•PBPK modeling was used to predict pharmacokinetics from rats to humans

•PBPK modeling was the tool used to predict malathion exposure across different life stages.

•Results of this PBPK modeling will impact the risk assessment for Ovide™.

•First time this approach has been used applied to the risk assessment of a pharmacological agent.

•This exercise allowed for the creation of a template model which can be used for other pesticides.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SOLVING AGENCY PROBLEMS